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The Cost of Sepsis

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Summary

Doctors Moerer and Burchardi review studies into costs of sepsis and cost effectiveness of treatments, highlighting the need for more research to support future clinical and financial decision-making.

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Despite great efforts in clinical research, a better understanding of the underlying pathophysiology, and new therapeutic approaches including drugs and supportive care, severe sepsis remains a serious health care problem. Each year approximately 750,000 patients in the USA suffer from severe sepsis. Due to the frequency and the expense of the treatment, sepsis consumes considerable resources resulting in a significant national socioeconomic burden. Severe sepsis has been estimated to generate costs of \$16.7 billion in the USA annually. Thus, this complex and life-threatening disease has been identified as a high cost driver not only from the ICU, but also from the hospitals' and society's perspectives. To improve the outcome of severe sepsis, innovative drugs and treatment strategies are urgently needed. Some drugs and strategies already offer promising and cost-effective results and will probably play a major role in the future. This article summarizes studies focusing on the evaluation of direct or indirect costs of sepsis and the costeffectiveness of new therapies for sepsis.

Introduction

Sepsis and septic shock are among the leading causes of death in critically ill patients [1, 2]. The economic burden of this disease is tremendous; for example the annual cost in the USA is estimated at \$16.7 billion [3]. Besides the high ICU or hospital costs for treating these patients, indirect costs due to productivity losses resulting from temporary or permanent morbidity and mortality are considerable. A wide variation of prevalence and incidence of severe sepsis and sepsis associated mortality have been reported in the literature [2]. Mortality is influenced by the severity of sepsis together with age, comorbidities and primary site of infection. Despite great efforts to understand the underlying pathophysiology and to improve diagnostic procedures and therapeutic concepts, the mortality of sepsis remains high with 30-50%, and up to 80% in septic shock, dying from the disease [3-7]. It is estimated that 2 - 3% of ward patients and 10 - 15% of ICU patients develop severe sepsis or septic shock. In the USA about 750,000 patients per year suffer from this systemic inflammatory response to infection causing 200,000 deaths from this complication [3]. For Germany the frequency of severe sepsis cases per year has been estimated to be between 44,000 and 95,000 [8]. Even if mortality has been reduced over recent years [9], it is still unacceptably high. As the general population progressively ages and technology produces further support and prolonged life, the frequency of sepsis will probably increase [2, 3].

innovative and expensive therapies. Besides the therapeutic efficiency of these therapies, the cost-effectiveness will play a major role in the future. However, even if the therapeutic effect and overall cost effectiveness has been proven, the possible risk remains that new products become excluded from clinical therapy solely because they add extra costs.

Due to the incidence of sepsis and the expensive effort of treating such patients, sepsis consumes considerable health care resources [10]. Unfortunately, there are still only a few studies analysing the direct costs of severe sepsis. The lack of standardised models for determining the cost of intensive care [11], and the inadequate documentation of intensive care unit (ICU) actions [12] prevent fast and easy evaluation of the cost of treating severe sepsis in intensive care. The majority of studies on ICU costs use top down methods by which consumed resources are averaged across all patients [11]. Costs of specific subgroups of ICU patients or even the variation of costs among individual patients [13], however, can only be assessed using bottom-up analysis [14, 15]. For example, the considerable costs for antibiotic therapy in infected patients are not attributable to direct drug costs alone. Depending on the given drug, an additional 8 – 33% of the expenditure can be caused by disposables, administration systems and time spent on administration [16].

Direct ICU Costs and Economic Impact of Innovative Therapies

Intensive care medicine, currently representing one of the largest clinical cost centres in hospitals, is supposed to be a major factor in the increase of health care costs [17, 18]. Expenses for intensive care are difficult to determine, but have been estimated to be up to 20% of a hospital's budget [2]. Within the ICU patient population, a small group is responsible for a disproportionately high amount of resource consumption [17-19]. Besides higher daily resource use, the main reason is the longer length of stay resulting in high personnel and overhead costs [10, 20, 21], which are responsible for 40 – 70% of total ICU costs. Oye and Bellamy [17] described an increase of costs related to the severity of illness (APACHE II) on admission to the ICU. They differentiated two groups of ICU patients. A relatively small group of high cost patients (8% of the ICU population) consume almost 50% of ICU resources compared to a large low cost group (92% of patients) consuming the other 50%. Another study showed similar results with 10% out of 10,606 patients admitted to an ICU accounting for 48.7% of ICU days and 50% of total ICU costs [18]. Such patients not only suffer from a higher severity of illness, but also higher frequency of infections and sepsis [20, 22]. We showed that among 10% of our patients with the highest total direct variable costs, 72% suffered from an infection [22]. Comparing infected with non-infected patients, resource consumption of mean daily direct variable costs (\bar{x} 397 vs. \bar{x} 305) and total direct variable costs (\bar{x} 14,507 vs. \bar{x} 3,985) were significantly increased with the presence of infections. In a recent German cost analysis, Neilson et al. showed that a small group of patients (3% percent out of 1,631 ICU patients) with a length of stay longer than 20 days was responsible for expending 22% of total ICU costs. Within these high cost patients 79% fulfilled the criteria of sepsis [19]. Patient related ICU costs for septic patients have been analysed by Edbrooke and colleagues in 213 patients from a university hospital in Sheffield, UK [21]. In non-septic patients median total costs were \$US 1,667 (US\$ 755 per day) compared to US\$ 10,623 in patients with sepsis. Median total costs per patient were twice to eleven fold higher (US\$ 3,802 – 17,963) compared to those without sepsis with daily cost between US\$ 931 and US\$ 1,079 per patient. According to a retrospective analysis of 385 patients with severe sepsis from three university hospitals in Germany, the average cost per patient was \bar{x} 23,297 (\bar{x} 1,318 /day) [10]. Mortality of these sepsis patients was 43% in the German study compared to 53% in the UK study. The length of stay of septic patients was significantly longer in both studies compared to non-septic patients. Besides the increased daily resource consumption, length of therapy and personnel costs are the main causes of these expenses. The reason for admission further influenced total ICU costs, with surgical patients being more expensive than medical or neurological patients. We also found higher costs in nonsurvivors compared to survivors, which has also been shown in earlier studies [3, 23, 24]. The greater costs in the German study may be due to a higher rate of trauma patients, but even on a national basis there is a large variation in resource use and total costs in patients with severe sepsis [25].

New Drugs

Sepsis therapy is based on three main principles, causal treatment (surgical and interventional treatment, antibiotic therapy), supportive therapy (ventilation, renal replacement, haemodynamic stabilization, enteral or parenteral nutrition, maintenance of homeostasis) and adjuvantive therapy (glucocorticoid or non glucocorticoid anti-inflammatory therapies) [26, 27]. Up to now, drug costs were mainly based on supportive or antibiotic therapy [10]. New therapeutic strategies such as intensive insulin treatment, early goal directed therapy or low dose glucocorticoid therapy have already reduced mortality [28-30], although cost-effectiveness has not yet been analysed.

During the last ten years, developments in sepsis treatment have focused on drugs designed to stop the inflammatory response and imbalance of haemostatic systems [31, 32]. A variety of these antiendotoxin and anticytokine strategies, such as NORASEPT, INTERSEPT and NORASEPT II, have failed to prove beneficial to the outcome [33-37]. Recently the MONARCS study showed an improvement of survival if patients were treated with a monoclonal TNF antibody [38], but pharmacoeconomic data is lacking.

In the PROWESS study it was shown that recombinant human activated protein C (Drotrecogin alfa (activated))

with antithrombotic, profibrinolytic and anti-inflammatory properties was able to significantly reduce mortality in patients with severe sepsis (19.4% adjusted relative risk reduction) [39]. This drug has been approved for use in high risk patients with multiple organ dysfunction or high APACHE II scores > 25. The succeeding ADDRESS study aimed to evaluate the drug's effectiveness in patients with lower severity of illness (APACHE II score < 25 or single organ failure), but has recently been stopped following interim analysis showing no positive effect. The cost-effectiveness of Drotrecogin alfa (activated) (rhAPC) has been analysed in several studies [40-43]. Assuming a unit price of \bar{x} 237.50, the additional average cost of rhAPC will be around \bar{x} 7,400 per treatment. According to Neilson et al. the total cost of treatment per patient was \bar{x} 26,400 compared to \bar{x} 18,100 for septic patients not being treated with this drug [43]. The cost-effectiveness was calculated at \bar{x} 14,100 per life year gained and thus comparable to other life saving health care interventions [43].

A therapeutic strategy need not be cost saving to be validated as cost-effective, but it must offer a benefit that is worthy of its expenditure [23]. The actual problem of introducing innovative drugs is that a proven benefit or cost-effectiveness does not necessarily lead to clinical use with patients. In times of limited budgets, we might be forced to withdraw high cost patient therapies to avoid restrictions in standard ICU therapy. Thus, a fair reimbursement for high cost innovative therapies must be established if such innovations are to be introduced into clinical practice.

Overall Hospital and Longterm Costs of Sepsis

Besides expenditures for intensive care, there are further costs attributable to severe sepsis. Lucioni et al. found that hospital costs are nearly doubled in cases of severe sepsis or septic shock [44]. In a Canadian study hospital costs of 100 patients with severe sepsis were analysed retrospectively [45]. ICU cost caused 38% of the total costs (CAD\$ 11,474 per patient). Letarte et al. estimated annual costs of CAD\$ 151.4 million for severe sepsis for the region of Quebec. Angus et al. calculated the costs of care in patients with severe sepsis mainly on the basis of hospital charges [3] and estimated the national incidence of sepsis. They identified severe sepsis in 192,980 cases, which yields 751,000 national cases per year and 2.26 cases per 100 hospital discharges. The average costs per patient were \$US 22,100 (average length of stay 19.9 days, mortality 28.6%). Severity of illness, reason for admission, age and gender were related to the costs. For Austria an incidence estimate of 6,700 – 9,500 cases per year yielded mean total direct costs of \approx 192 to 272 million [46].

Relatively little is known about long-term clinical and economic outcome in patients with sepsis. Quartin found that 30-day survivors of sepsis had a life expectancy of only about one-half of that expected based on their comorbidities [47]. Based on data from a large U.S. health insurance claims database, Weycker et al. estimated long term mortality and medical care charges over a follow up period of 5 years for patients with severe sepsis [48]. They found that the economic burden of this disease is high not only during the period of acute hospitalization, but also over the following years. Overall mean cumulative charges more than doubled from mean US\$ 44,600 on index admission to US\$ 118,800 after five years and were highly dependent on age, comorbidities, and severity of sepsis (number of organ failures). Unfortunately Weycker et al. did not include a control population and therefore the incremental costs of severe sepsis could not be estimated.

Indirect Costs

Sepsis also causes significant indirect costs, as a consequence of productivity loss caused by absence from work, disability with premature retirement and mortality. Data on the absence and disability related to unpaid labour are very scarce. It is almost impossible to measure these indirect costs of disease and most studies are estimates based on mathematical models calculating the resulting financial burden on the society. In Austria, based on 6,700 to 9,500 cases per year indirect costs of severe sepsis were estimated to be between \approx 484 million and \approx 686 million [46]. In Germany, with calculations for temporary morbidity (\approx 3,432/ patient), permanent morbidity (\approx 10,159 per patient) and mortality (\approx 46,000/ per patient) based on 44,000 to 95,000 estimated cases of severe sepsis, the total indirect costs are supposed to be \approx 2,622 – 5,660 million [8]. According to Schmid et al. Hospital costs are only responsible for 28% of all costs attributable to severe sepsis [8].

Conclusion

Patients with severe sepsis have a high mortality rate, spend longer in the ICU, and are more expensive to treat than nonseptic patients. Sepsis remains one of the leading causes of death in intensive care units and causes a high economic burden for the society due to direct and indirect costs of illness. Data on the direct and indirect costs of severe sepsis are still scarce and comparisons between existing studies are difficult due to different methodological approaches (for example cost versus charges). Thus, there is an urgent need for cost and incidence studies on sepsis, especially when innovative and expensive therapies are being introduced. Nevertheless, all published studies show that direct ICU and hospital costs are high primarily due to increased length of ICU and hospital stay. The new therapeutic approaches such as Drotrecogin alfa (activated) are promising, but more research is required to improve outcome in septic patients. Besides the therapeutic efficiency of these therapies, cost-effectiveness will play a major role in the future. In times of limited financial resources clinicians and health care providers will be forced to weigh up costs and the expected benefits carefully.

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